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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,402	06/30/2006	Yoram Groner	85189-12200	8368

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EXAMINER	
SGAGIAS, MAGDALINE K	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,402	GRONER ET AL.	
	Examiner	Art Unit	
	MAGDALENE K. SGAGIAS	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,13 and 49-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,13 and 49-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/13/08 has been entered.

Applicant's arguments filed 2/13/08 have been fully considered but they are not persuasive. Claims 1-9, 13, 49-51 are pending and under consideration. The amendment has been entered. Claims 10-12, 14-48 are canceled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 13, 49-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-9 are directed to a method for upregulating runt-related transcription 3 factor (RUNX3) expression in a subject, which comprises delivering an active agent to immune cells of said subject having low activity or no activity of RUNX3 gene product, wherein the active agent induces expression or over-expression of RUNX3 in said immune cells of said subject, thereby inhibiting the proliferation of T-cells in said subject. Embodiments limit the immune cells to

thymocytes and dendritic cells (DC). Embodiments limit the active agent, to a polynucleotide encoding RUNX3 and further limitations, wherein the delivery step is performed ex vivo. Claim 13 is directed to a method for reducing the proportion of mature dendritic cells versus immature dendritic cells in a subject comprising: delivering an active agent to immune cells in a subject having low activity or no activity of RUNX3 gene product, wherein said active agent, induces expression or over-expression of RUNX3 in said immune cells of said subject, thereby reducing the proportion of mature dendritic cells versus immature dendritic cells in said subject.

The specification teaches LPS or using other DC maturation-inducing-reagents induced maturation of WT DC, reflected in elevated surface expression levels of MHC II and CD86 (FIG. 6B, C). This LPS induced maturation was significantly more pronounced in the KO DC (FIG. 6B, C). The specification also teaches RUNX3 KO DC were significantly more efficient stimulators of CD4+ T-cell proliferation compared to WT DC (FIG. 6E) [00141]. However, the specification fails to provide sufficient guidance to correlate the ability of LPS to induce maturation of knock out DCs or the ability of WT and KO DC that stimulate T cells in vitro to delivering an active agent to immune cells in a subject having low activity or no activity of RUNX3 gene product resulting in overexpression of RUNX3 in the immune cells of a subject, thereby inhibiting T-cell proliferation in said subject. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed methods for upregulating RUNX3 expression in a subject by way of the claimed methods. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

The claims are directed to delivering an active agent to immune cells of said subject having low activity or no activity of RUNX3 gene product, wherein the active agent induces expression or over-expression of RUNX3 in said immune cells of said subject, thereby inhibiting

the proliferation of T-cells in said subject. The specification teaches agents such as LPS, TNF alpha and anti CD40 antibodies as efficient stimulators CD4+ T-cell proliferation of RUNX3 knock out dendritic cells compared to WT dendritic cells in vitro [0140] [0141]. The specification further contemplates compositions for inhibiting T cell-mediated inflammation comprising as an active ingredient an agent that induces up-regulation of RUNX3 expression in cells [0021]. The specification contemplates compositions for inhibiting T cell-mediated inflammation are useful in situations where it is desirable to down-modulate an immune response, for example in a transplant patient or a subject suffering from an autoimmune disease including but not limited to systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and other forms of arthritis, multiple sclerosis (MS), ulcerative colitis, Crohn's disease, pancreatitis, diabetes, psoriasis, or other disorders associated with an abnormal immune response [0021]. However, the specification fails to provide guidance to correlate LPS, TNF alpha and anti CD40 antibodies that are efficient stimulators CD4+ T-cell proliferation of RUNX3 knock out dendritic cells compared to WT dendritic cells in vitro to delivering such agents to immune cells with such phenotype in vivo resulting in overexpression of RUNX3 in the targeting immune cells, thereby inhibiting the proliferation of T-cells in vivo. The delivery of an agent to tissue culture cells does not provide guidance for overcoming the obstacles of in vivo delivery because the agent does not have to pass through the complex organization of organs and tissues. Cell cultures do not mimic organs in that there is no 3-D structure, blood vessels, connective tissue through which the agent would need to pass in vivo. Second, the specification while provides guidance for the LPS, TNF alpha and anti CD40 antibodies as efficient stimulators CD4+ T-cell proliferation of RUNX3 knock out dendritic cells compared to WT dendritic cells in vitro, does not provide guidance for the full breadth of all types of agents. It is known that agents have It is not known whether any target at any dose and at any route of administration would in vivo would be able to

target immune cells having low or no activity of RUNX3 will induce expression of RUNX3 thereby inhibiting T cell proliferation in vivo. This is because the agents have to pass through vascular, tissue and organ barriers in vivo to target immune cells thereby challenging the route and dose of agent required to induce expression or overexpression of RUNX3 thereby inhibiting the proliferation of T cell in vivo. Moreover, **Rothenberg et al,** (Annu Rev Immunol, 23: 601049, 2005) note the three mammalian Runx factors are all expressed in the thymus and used throughout T cell development, although they are not T cell specific in expression or function (p 612, 2nd paragraph). **Coffman** (Cell Biology International, 27: 315-324, 2003) notes in mammals, Runx proteins are protooncogenes and tumor suppressors (P 321, 1ST paragraph). Coffman notes that the role of RUNX3 in cell proliferation is unclear. Independent studies from two different labs have demonstrated that *Runx3* knockout mice manifest severe limb ataxia due to defective development of proprioceptive neurons in the dorsal root ganglia (p 318, 1st column, last paragraph). In another study *Runx3* knock out mice displayed hyperproliferation and suppressed apoptosis of epithelial cells in the gastric mucosa, and died shortly after birth apparently due to starvation (p 318, 1st column, last paragraph). However, this phenotype was not found in the *Runx3* knockout mice produced by Levanon et al in 2002, (Coffman, p 318, 1st column, last paragraph). The reason for the discrepancy between the different *Runx3* knockout phenotypes is not clear (p 318, 1st column, last paragraph). As such the specification fails to provide guidance to overcome the issue of an agent specifically inhibiting T cell proliferation by overexpression of RUNX3 in immune cells where RUNX 3 may act as either a tumor suppressor or as an oncogene as stated by the art.

The specification teaches increased RUNX3 expression in the pulmonary macrophages of an ova-induced acute asthma mouse model (specification p 33-34, Figure 3.1). However, the specification has failed to correlate the increased RUNX3 expression in the ova-challenged

mice to the delivery of RUNX3 polynucleotide by any route of administration in vivo that induces overexpression of RUNX3 to the immune cells, inhibiting the proliferation of T-cells resulting in the treatment of a T-cell mediated inflammation. The specification also teaches perturbed distribution of CD4+/CD8+ T lymphocytes, increased ratio of mature to immature dendritic cells, increased levels of IL-5 and development of asthma-like symptoms in the RUNX3 knock out mice. However, the specification has failed to correlate the perturbed distribution of T cels in RUNX3 knock out mice to the delivery of RUNX23 polynucleotide in wild type mice where overexpression of RUNX3 in the immune cells of the wild type mice will inhibit T cell proliferation and treat a T cell mediated inflammatory disorder.

The specification teaches that RUNX3 k/o mice develop perturbed distribution of CD4+/CD8+ T lymphocytes, increased ratio of mature to immature dendritic cells, increased levels of IL-5 and development of asthma-like symptoms. The specification fails to correlate the perturbed distribution of CD4+/CD8+ T lymphocytes and the increased IL-5 levels to contacting cells with a polynucleotide encoding RUNX3 in vivo, wherein increased expression of RUNX3 will mediate a T cell-mediated or IL-5 mediated inhibition of inflammation. IL-5 is involved in the Th1/Th2 pathway of inflammatory diseases up regulating antibody formation via B cells and eosinophils (**Kidd,** Alternative Medicine Review, 8(3): 223-246, 2003) (p 225, figure 1). In inflammatory diseases T cell proliferation or Th2 proliferation is associated with interferon gamma secreted by the Th1 cells, where interferon gamma inhibits proliferation of Th2 cells (**Kidd,** Alternative Medicine Review, 8(3): 223-246, 2003) (p 225, figure 1). The art also teaches that, distinct from IL-5, novel or cytokines such as IL-9, IL-11, IL-13 and IL-25, are likely important in an inflammatory disease in regulating the Th1/Th2 pathway involved in T cell proliferation (Kidd p 234, 2nd column, 3rd paragraph). The specification has not provided evidence to correlate the perturbed distribution of CD4+/CD8+ T lymphocytes and the increased

IL-5 levels in the RUNX3 k/o mice to increased expression of RUNX3 by contacting cells with a polynucleotide encoding RUNX3 resulting in inhibition of T cell proliferation in a subject in need thereof. However, the specification failed to provide guidance to correlate the increased IL-5 levels and the perturbed distribution of CD4+/CD8+ T lymphocytes in the RUNX3 k/o mice to the Th1/Th2 cytokine inflammatory biology of other species, as for example humans. The art teaches that some of the most important variables in the Th1/Th2 cytokine biology of inflammatory diseases include the species being researched, whether studies are done in vivo or ex vivo (**Kidd**, p 226, 1st column, 2nd paragraph). **Walsh** (Current Pharmaceutical Design, 11: 3027-3038, 2005) reports that disappointing results with humanized anti-IL-5 mAbs casts doubts on the role of the eosinpophil in asthma (p 3030, 1st column, last paragraph) and eosinophils are important in pro-inflammatory cells in asthma pathogenesis rather than inflammatory cells. Thus, the specification has not taught how increased levels of IL-5 in the Runx3 k/o mice relate to T cell proliferation and increased eosinophilia and whether the introduction of RUNX3 in the k/o mice will result in the inhibition of inflammation by regulating eosinophilia thru the Th1/Th2 pathway. At the time of the instant invention asthma is largely a Th2-driven disease, but much of this story is incomplete (Kidd, p 234, 2nd column, last paragraph).

With regard to delivering a polynucleotide encoding RUNX3 (RUNX3 gene therapy), in vivo, wherein increased RUNX3 expression thereby inhibiting T cell proliferation iv vivo as contemplated by the specification the state of the art for inhibiting T cell mediated inflammation by gene therapy is unpredictable. In general, with regard to the gene therapy, while progress has been made in recent years for gene transfer in vivo, vector targeting to desired tissues in vivo continuous to be a limitation as supported by numerous teachings in the art. Numerous factors complicate the gene delivery art, which would not have been shown to overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution,

rate of clearance into tissues, etc), the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRMA produced, the stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically on the vector being used and the protein being produced. While progress has been made in recent years for in vivo, gene transfer, vector targeting in vivo to desired organs continuous to be unpredictable and inefficient. **Zhou et al,** (Medicinal Research Reviews, 24(6): 748-761, 2004) even after the filing of the instant application indicates that gene therapy requires gene systems with less toxicity and immunity, high efficiency in gene transfer and the therapeutic gene expression in the targeted cells or tissues at functional level in a controllable manner (p 748, last paragraph). Zhou also notes to date, however, the gene delivery systems, including non-viral and viral vectors have somewhat immunogen inducing the host immune responses in gene therapy, which is one of the challenges of gene therapy (p 749, 1st paragraph). Zhou teaches that despite considerable progress over the past decade in the generation of gene transfer systems with reduced immunogenic properties, the remaining immunogen of many gene therapy vectors is still the major hurdle preventing their application in clinical trials, because the host immune responses induced by immunogen of the vectors lead to low level and short term of transgene expression, inefficient re-administration of the same vectors and severe side-effects in clinical trials (p 752, last paragraph). Zhou teaches that mice injected either intraperitoneal, intravenous or subcutaneously with rAAV-OVA developed strong OVA-specific CTL response, however, mice injected intramuscularly with the same virus developed minimal CTL response (p 755, 2nd paragraph). The specification however, has not provided any specific guidance or teachings with regard to the other modes of cell targeting or modes of administering

RUNX3 therapeutic gene encompassed by the claims. With regard to the contact between the cells and the polynucleotide encoding RUNX3 is performed ex vivo, the art teaches that the purity of DC produced in vitro is questionable, and cultures could contain DC in different stages of development or other unknown contaminant cell types (**O'Neil et al**, Journal of Leukocyte Biology, 75: 600-603, 2004) (p 602, 2nd column, last paragraph). DC produced from different starting cell populations, such as monocytes and BM or cord blood can vary in their functional capacity (p 602, 2nd column, last paragraph).

As a second issue, claim 13 is directed to delivering an active agent to immune cells of a subject having low or no activity of RUNX3 gene product, resulting in inducing expression of RUNX3, thereby reducing the proportion of mature DCs versus to immature DCs in the subject. The specification teaches increased ratio of mature to immature dendritic cells, in the RUNX3 k/o mice associated with asthma-like symptoms and inflammatory diseases. However, the specification fails to provide guidance to correlate the increased ratio of mature dendritic to immature dendritic cells in the k/o mice to the delivery of an active agent for inducing expression of RUNX3 in immune cells thereby reducing the proportion of mature DCs to immature DCs in the subject. For example, in pulmonary inflammatory diseases, the art teaches that a more detailed phenotypic analysis of dendritic cells in their role of inflammatory processes in the pathogenesis of pulmonary arterial hypertension (PAH) need to be performed (**Lambrecht et al**, Eur Respir J, 29: 435-437, 2007) p 436, 2nd column, last paragraph). The lack of significant effects of systemic steroids in idiopathic PAH patients provides an argument against the role of DCs in PAH (**Lambrecht**, p 436, 2nd column, last paragraph). **Lambrecht et al**, reports that the most important question even in 2007 is what is the functional role of dendritic cells in PAH (p 436, 1st column, 2nd paragraph). **Wallet et al**, (Clinical Medicine & Research, 3(3): 166-178, 2005) reports that the molecular targets of TGF-beta mediated suppression in DCs remain ill

defined and one such target appears to be the RUNX3 transcription factor (p 170, 1st column, 2nd paragraph). **Wallet et al,** (Clinical Medicine & Research, 3(3): 166-175, 2005) indicates that primarily a contrasting role of DCs has been described as a function of maturation where immature DCs were largely considered to be non-inflammatory or tolerogenic, but mature dendritic cells were considered capable of eliciting a pro-inflammatory immune responses and although generally correct, this paradigm is now proving too simple (p 166, 1st column). This issue is further complicated by the identification of distinct subtypes of dendritic cells that exhibit different antigen-presenting cell effector functions (abstract).

In light of the above, the state of the art is suggesting that that the role of RUNX3 in cell proliferation is unclear and thus overexpression of RUNX3 by an agent in vivo might be feasible in the future. The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of an agent crossing the in vivo vascular, tissue or organ 3D barriers resulting in inhibiting T cell proliferation in vivo raised by the state of the art. Therefore, the skilled artisan would conclude that the state of art of RUNX3 inhibiting T cell proliferation in vivo is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for upregulating RUNX3 expression in immune cells of a subject by delivering an agent in vivo without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for delivering a agent to immune cells, thereby inducing overexpression of RUNX3 in the immune cells, thereby inhibiting T cell proliferation in vivo, the lack of direction or guidance provided by the specification for delivering a agent to immune cells, thereby inducing overexpression of RUNX3 in the immune cells, thereby inhibiting T cell proliferation in vivo, the unpredictable state of the art with respect to delivering a agent to immune cells,

thereby inducing overexpression of RUNX3 in the immune cells, thereby inhibiting T cell proliferation in vivo, the undeveloped state of the art pertaining to delivering a agent to immune cells, thereby inducing overexpression of RUNX3 in the immune cells, thereby inhibiting T cell proliferation in vivo, and the breadth of the claims directed to all agents, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Applicants argue the presently claimed invention is based on studies using both RUNX3 knock out (KO) mouse and RUNX3 wild-type (WT) mice. Unlike the WT mice, the KO mice are homozygous for the RUNX3 null allele, wherein the wild type copy of the RUNX3 gene undergoes target disruption resulting in the prevention of the expression of the RUNX3 gene. The WT mice, on the other hand, already contain endogenous copies of the RUNX3 gene in their genome and are used in place of those mice that would have been delivered with the RUNX3 polynucleotide, as described in the specification. Accordingly, both RUNX3 WT and KO mice are employed to show the importance of RUNX3 expression in mediating T cell-mediated inhibition of inflammation.

These arguments are not persuasive because the studies in RUNX3 knock out mice cannot be correlated with delivering an agent in vivo by way of the claimed methods in vivo resulting in overexpression of RUNX3 in immune cells, thereby inhibiting T cell proliferation in vivo. As discussed above the in vitro data of RUNX3 knockout cells cannot be extrapolated into in vivo.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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